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Amlodipine-induced gingival hyperplasia

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ABSTRACT

Calcium channel blockers (CCB) are the best-known, most widely used drugs in the treatment of hypertension in the world. Gingival hyperplasia is one of the uncommon side effects of CCB usage. Among CCBs, it's most commonly seen due to nifedipine. Gingival hyperplasia is rarely seen with the use of amlodipine. The mechanism of drug-induced gingival enlargement is not entirely understood, but it's clear that it is due to multifactorial influences. Although the pharmacologic effect of each drug is different, all of them are estimated to act similarly to the secondary target tissue, i.e., the gingival connective tissue, thus resulting in common histopathological findings. Both inflammatory and non-inflammatory mechanisms are involved. This case has been presented to emphasize that the development of gingival hyperplasia in patients with hypertension could be a side effect of amlodipine usage.

Keywords: Gingival hyperplasia; amlodipine; side effect

Gingival hyperplasia is an enlargement of the tissue in the shape of a pyramid located between the teeth. Gingival hyperplasia is rarely encountered in clinical practice. The common causes of gingival hyperplasia are drugs, heredity, non-Hodgkin's lymphoma, acute monocytic leukemia, granulomatous diseases, fibroma, lipoma, malign melanoma, and chronic periodontal infections. However, drug assumption is the most common.[1] The three main drugs inducing gingival overgrowth (DIGO) are anticonvulsants and immunosuppressive and antihypertensive agents. Although the pharmacologic effect of each drug is different, all of them are estimated to act similarly to the secondary target tissue, i.e., the gingival connective tissue, thus resulting in common histopathological findings. Both inflammatory and noninflammatory mechanisms are involved.[2] The incidence of gingival hypertrophy with CCB, especially nifedipine treatment, has been shown to be as high as 20%, and this rate is much higher than amlodipine-induced gingival hyperplasia. It has been hypothesized that these patients have abnormal sensible fibroblasts to the drug. It has been shown that fibroblasts from the overgrown gingiva of these patients are characterized by elevated levels of protein synthesis and decreased collagenase activity, and, finally, accumulation of protein in the gingiva, especially collagen. Amlodipine is a long-acting dihydropyridine calcium antagonist frequently used for the treatment of hypertension and angina. Its effect is inhibited by the transmembrane influx of calcium ions into the smooth and cardiac vascular muscles. Although various adverse effects of amlodipine, like headache, edema, dizziness, flushing, and palpitations, have been reported, gingival overgrowth is rarely seen.[3]

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CASE

A 40-year-old woman presented in our outpatient clinic with a complaint of painless swollen gums. The patient was referred to our clinic by her dentist with the pre-diagnosis of a drug-induced adverse effect. Gingival overgrowth involved the interdental papilla and marginal gingiva localized on the anterolateral facial surface of the labial maxillary and mandibular gingiva. History revealed that the patient was diagnosed with hypertension nine months previously, and amlodipine (5 mg) was prescribed. She did not have any addictions, drug usage, allergies, or significant family history of any critical diseases. At three months, she noticed painless gingival enlargement. She previously applied to the dental clinic for this complaint and was referred to our clinic. There wasn't any specific physical finding except the gingival overgrowth (figure 1).

Poor oral hygiene was observed. Her vital signs were within the normal range. Complete hemogram, biochemical kidney, liver function tests, fasting glucose, lipid profile, serum electrolyte levels, and thyroid function test were done, and all the parameters were in the normal range. Her physical examination showed no peripheral and cervical lymphadenopathy, hepatosplenomegaly, or B symptoms. Herewith, we exclude malignant diseases. The medication was replaced with ramipril 10mg/day, and the patient followed for two months. A marked reduction of gingival overgrowth was evident two months after the withdrawal of amlodipine (figure 2).

Thus, the diagnosis of amlodipine-induced gingival overgrowth (AIGO) was confirmed. There is no more need for gingival biopsy, surgical intervention, and gingivectomy. The patient's dentist followed up with oral cleaning, scaling, and monitoring of gingival status. A patient has given us written permission to write this case report.

DISCUSSION

Especially three classes of drugs are accused of drug-induced gingival overgrowth. Among these drugs, the most ordinary cause of DIGO is diphenylhydantoin. Nifedipine is the most common CCB associated with gum enlargement, although other agents implicated include verapamil, felodipine, nitrendipine, diltiazem, and amlodipine.[2,4]

Amlodipine is a dihydropyridine CCB that is commonly prescribed as an antihypertensive drug. The prevalence of AIGO has been reported to be 1.7%-3.3%. The incidence of gingival hypertrophy with nifedipine treatment is as high as 20%, and a 2002 study reported that the prevalence with the use of CCBs could be nearly 38%.[5,6] In the United States of America, Jorgensen estimated the prevalence of gingival hyperplasia caused by amlodipine in 1997 to be 3.3% for patients. Also, a study conducted in India in 2014 by Tejnaniet al. found a similar number of 3.4%.[3,7] This suggests that the prevalence of AIGO is similar across populations of dissimilar races and geography and has stayed stable over time.

It was known that CCBs such as nifedipine could cause gingival hyperplasia. When amlodipine came into the market, there were also similar reports of amlodipine-induced gingival hyperplasia. This was first reported by Ellis et all in 1993.[8] This side effect is three times more common in males. AIGO is generally started at the dose of 10 mg/day within three months

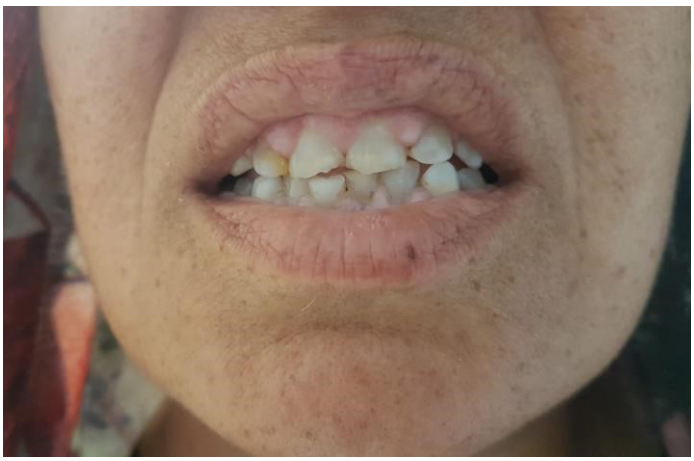

Figure 1. The patient's gingival view during amlodipine treatment

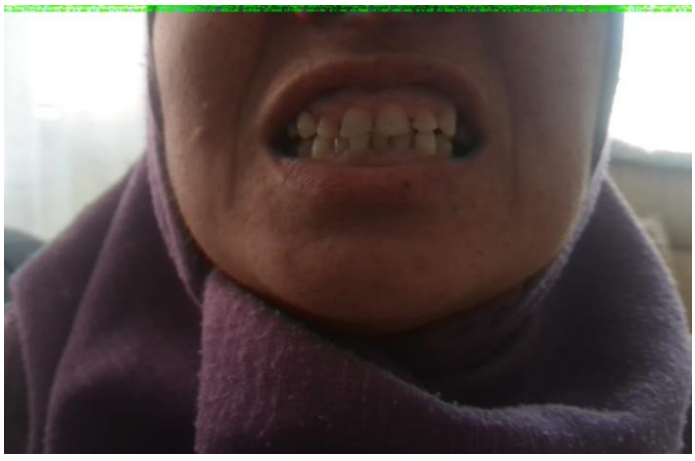

Figure 2. The patient's gingival view after withdrawal of amlodipine treatment

of drug initiation.[3] Although few cases of AIGO have been reported, our case is interesting as it occurred with a low dose of amlodipine (5 mg), and our case was female.

The etiology of DIGO is not entirely understood, but it is now known that a multifactorial role could be involved in its cause. With this, the effect of age, sex, duration, and dosage of the drug on the pathogenesis of gingival overgrowth is not clearly understood. Current studies have investigated the pathogenesis of these drugs' direct and indirect effects on the gingival fibroblast mechanism. It has been hypothesized that these individuals have abnormally sensible fibroblasts to the drug. It has been shown that fibroblasts from the overgrown gingiva of these patients are characterized by elevated levels of protein synthesis, especially collagen.[9] A unifying hypothesis states that anticonvulsants, immunosuppressive agents, and CCBs all cause cation of flux inhibition. Decreased cation influx of folic acid activate transfer within gingival fibroblasts causes diminished cellular folate uptake, which decreases the synthesis and activation of matrix metalloproteinases, a group of enzymes responsible for collagen breakdown. This reduces collagenase activity, causing decreased degradation and, thus, connective tissue accumulation, eventually presenting gingival overgrowth. Also, periodontal hygiene appears to play a significant role in gingival hyperplasia. Bacterial plaques allow the concentration of drugs in the build-up area and produce an inflammatory state, leading to increased fibroblast proliferation, which assists in DIGO formation.[9,10] Substituting the drug amlodipine with another antihypertensive remains the basis of management. Supplements of folic acid and ascorbic acid are also recommended. Reduction in the size of gingival overgrowth has been reported within a week of drug withdrawal and may lead to complete resolution.[2] Patients benefit from effective oral hygiene measures, professional tooth cleaning, scaling, and root planning. If gingival enlargement persists after carefully considering previously mentioned approaches, these cases must be treated by either gingivectomy or flap surgery. [2,5,6] In our patient, substituting the drug amlodipine with ramipril was enough. Gingivectomy or other surgical interventions were not performed. The patient's dentist followed up with oral cleaning, scaling, and monitoring of gingival status.

Finally, we emphasize that gingival overgrowth could be a side effect of amlodipine even with a very short-term, low-dose administration and in females. Physicians and dentists should be aware of the etiologic medications that can induce gingival hyperplasia and be able to identify changes in the oral cavity in such patients and to prevent, diagnose, and successfully manage them. Also, in this case, when CCB is started in patients with poor oral hygiene, informing the patient about these side effects will be beneficial in avoiding unnecessary examinations.

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